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FINITE DIMENSIONAL MODELS OF DRUG RESISTANT AND PHASE SPECIFIC CANCER CHEMOTHERAPY

The problem of modelling drug resistance and phase specificity of cancer chemotherapy using finite dimensional models were considered. We formulate optimal control problems arising in protocol design for such models and discuss research issues resulting from these formulations.

1. INTRODUCTION

Mathematical modelling of cancer chemotherapy has had more than four decades of history. It has contributed to the development of ideas of chemotherapy scheduling, multi-drug protocols, and recruitment. It has also helped in the refinement of mathematical tools of control theory applied to the dynamics of cell populations (e.g. [5], [21]). However, regarding practical results it has been, with minor exceptions, a failure. The reasons for that failure are not always clearly perceived. They stem from the direction of both biomedicine and mathematics: important biological processes are ignored and crucial parameters are not known, but also the mathematical intricacy of the models is not appreciated. Moreover, there exist many limiting factors and "probably the most important - and certainly the most frustrating - of these limitating factors is drug resistance" [12, pg. 335]. Cancer cells are genetically unstable and combined with fast duplications, mutations and amplifications of genes are but two of several mechanisms which allow for quickly developing resistance to anti-cancer drugs. Several probabilistic models for developing drug resistance exist in the literature (e.g. [3, 7, 9]) where the tumor size is analyzed as a stochastic process and some associated probability is maximized, like in [3] the probability to have no resistant cells. These models and their predictions can often be tested against clinical data and thus provide quantitative information. On the other hand, deterministic models for the evolution of the tumor under drug resistance based on the underlying probabilistic effects contribute to a qualitative understanding of the phenomenon. A simple model which only distinguished sensitive and resistant cells was given in [4]. The broad class of models which describe drug resistance due to gene amplification as a dynamic process and not as a single mutation event

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is represented by probabilistic [6, 7, 9, 10] or infinite-dimensional [11, 25, 27] models allowing only limited and sometimes mathematically not rigorous analysis. In this paper we formulate more detailed mathematical models for cancer chemotherapy under evolving drug resistance which are cell cycle specific and consider various degrees of drug resistance both for a single killing agent (section 1) and multiple drugs (section 2) but are finite dimensional. While the first model falls into a well researched class of problems mathematically, this is not the case for the second model leading also to interesting mathematical questions. We initiate an analysis of mathematical models for various cancer treatments with tools of modern optimal control in order to provide qualitative insights into the structure of optimal protocols some of which might not be so obvious and relatively difficult, or at least very expensive to test in a laboratory setting. At the same time interesting and important mathematical problems arise which are worthwhile to pursue on their own merit.

2. MATHEMATICAL MODELS FOR CANCER CHEMOTHERAPY WITH A SINGLE KILLING AGENT UNDER EVOLVING DRUG RESISTANCE

We describe two dynamical models of acquired drug resistance for a single killing agent based on the mechanism of gene amplification. The models are branching random walk type with a finite number of states [9], but averaged over the populations in individual compartments. Mathematically these models are described by single-input bilinear systems and fall into the class considered by us in earlier research ([14]-[19], [23]-[25]).

2.1. GENE AMPLIFICATION AND THE DYNAMICS OF DRUG RESISTANCE.

Amplification of a gene is an increase in the number of copies of that gene present in the cell after cell division, deamplification corresponds to a decrease in its number of copies. Cancer cells are genetically highly unstable and due to mutational events and gene amplification during cell division, cells can acquire genes which as a result make them more resistant to certain drugs, for example by addition of genes which aid removal or metabolization of the drug. The more copies of such a gene will be present, the more resistant the cells become to even higher concentrations of the drug. Gene amplification is thus well-documented as one of the main reasons for evolving drug resistance of cancer cells (see, for example, [10]). Taking into account an increasing degree of gene amplification leads to infinite-dimensional models [11] involving integro-differential equations which are difficult to analyze [22, 26, 27]. Thus, assuming some level of simplification and staying within a finite dimensional structure may enable a better analysis of these problems. Following this idea we present two finite-dimensional mathematical models describing developing drug resistance formulated by us which form the basis for some of the proposed mathematical investigations. The models are based on a one-copy forward gene amplification hypothesis (see [6, 7]), which states that in cell division at least one of the two daughter cells will be an exact copy of the mother cell while the second one with some positive probability undergoes gene amplifications.

2.2. A MODEL WITH TWO LEVELS OF DRUG RESISTANT CELL POPULATIONS.

As cancer cells obtain increasing numbers of copies of genes which aid removal or metabolization of the drug through gene amplification, the more resistant they become to increasingly higher concentrations of the drug. It is therefore natural to consider various levels of drug resistance in the model and divide the resistant population into compartments according to the degree of drug resistance of the cells. Here we formulate the simplest case when only two of these levels are distinguished, i.e. overall the model has three compartments consisting of drug sensitive, partially resistant and resistant cells. We denote the average numbers of cells in these compartments by S, P and R, respectively, and denote the inverse of the average transit times through these compartments by a, b and c. In the model only transitions between sensitive and partially resistant cells and between partially resistant and fully resistant cells are allowed.

If a sensitive cell undergoes cell division, the mother cell dies and one of the daughters will remain sensitive. The other daughter with probability q, $0< q< 1$, changes into a partially resistant cell. However, for cancer cells (and different from viral infections like HIV, for example, see [13]) it is possible that a resistant cell may mutate back into a sensitive cell by losing extra gene copies [1, 8]. Therefore, if a partially resistant cell divides, again the mother dies and one of the daughters remains partially resistant, but the second daughter with probability s, $0< s< 1$, undergoes gene amplification and becomes resistant or with probability r, $0\sim r< 1- s$, undergoes gene deamplification and becomes sensitive. The case $r= 0$ when this is excluded is called stable gene amplification while unstable gene amplification refers to the phenomenon $r> 0$. Finally, when a resistant cell undergoes cell division, one of the daughters may change back to partially resistant. This probability is the same as for partially resistant cells.

We now consider a cytostatic killing agent. Let u denote the drug dose, $0\sim u\sim 1$, with $u= 0$ corresponding to no drug being used and $u= 1$ corresponding to a full dose. It is assumed that the drug kills a fixed proportion u of the outflow of the sensitive cells at time t, aS(t), and therefore only the remaining fraction (1- u)aS(t) of cells undergoes cell division. Of these new cells then (2 - q) (1- u)aS(t) remain sensitive, while a fraction q(1- u)aS(t) mutates to partially resistant cells. The effectiveness of the drug on partially resistant cells is weaker, but not void yet, so we add a coefficient β, $0< \beta < 1$ to represent it. Thus only a portion of the outflowing cells from the partially sensitive compartment proportional to βu is killed by the drug and the surviving portion $(1- \beta u)bP$ undergoes cell division with one of the daughter cells possibly mutating. Thus, overall the controlled dynamics can be described by the following equations:

$$\dot{S} = - aS + (1 - u)(2 - q)aS + (1 - u)rbP, \qquad (1)$$

$$\dot{P} = - bP + (1 - u)(2 - r - s)bP + (1 - u)qaS + rcR, \qquad (2)$$

$$\dot{R} = - cR + (2 - r)cR + (1 - u)sbP. \qquad (3)$$

Here the first terms on the right hand sides account for the deaths of the mother cells, the second terms describe the return flows into the compartments and the remaining terms give the cross-over flows in the presence of a drug. Note that the effects of the drug show up at all return and cross-over flows except for the resistant compartment.

2.3. INCLUDING PHASE SPECIFICITY.

We expand the model above to include phase specificity in the sensitive and partially resistant compartments. The most commonly used killing agents are G_2/M phase specific. Therefore within the sensitive and partially sensitive compartments we combine the second growth phase G_2 and mitosis M into a second sub-compartment and group the remaining phases (G_0, G_1 and S) into a first sub-compartment. We denote the average numbers of cancer cells in these compartments by S_1, S_2, P_1 and P_2, respectively, and denote the corresponding inverse transit times of cells through these compartments by a_1, a_2, b_1 and b_2. Cells are killed in the second sub-compartments, i.e. all cells leave, but only the surviving ones reenter the cell cycle. The dynamics of the resistant compartment is not changed. A model which includes a G_2/M phase specific killing drug, partial and complete resistance of cancer cells to this drug while allowing for reverse or unstable gene amplification can therefore be described by

$$\dot{S}_1 = -a_1 S_1 + (1-u)(2-q)a_2 S_2 + (1-\beta u)rb_2 P_2, \qquad \dot{S}_2 = -a_2 S_2 + a_1 S_1, \tag{4}$$

$$\dot{P}_1 = -b_1 P_1 + (1-\beta u)(2-r-s)b_2 P_2 + (1-u)qa_2 S_2 + rcR, \quad \dot{P}_2 = -b_2 P_2 + b_1 P_1, \tag{5}$$

$$\dot{R} = -cR + (2-r)cR + (1-\beta u)sb_2 P_2. \tag{6}$$

2.4. MATHEMATICAL STRUCTURE OF THE MODELS WITH A SINGLE KILLING AGENT.

Both models are single-input bilinear systems. If, similarly as it is done in [22] more compartments are added to further differentiate the levels of drug resistance, or if blocking and/or recruiting agents (without additional killing effects) are modelled as well, then multi-input bilinear systems of the form arise.

$$\dot{N} = (A + \sum_{i=1}^{m} u_i B_i)N, \quad N(0) = N_0, \tag{7}$$

We therefore consider a general n-compartment model (7) for cancer chemotherapy as an optimal control problem over a fixed therapy interval with dynamics and objective of the form

$$J = kN(T) + \int_0^T qN(t) + \ell u(t)dt \to \min \tag{8}$$

where *k, q* and *l* are row-vectors of non-negative weights. The penalty term *kN(T)* represents an average of the total number of cancer cells at the end of an assumed fixed therapy interval [0, *T*], the term *qN(t)* models cumulative effects of the therapy, and the control term $\ell u(t)$ in the Lagrangian measures the negative side effects of the drugs, measured in a weighted L_1-type norms. Each control takes values in a compact interval in $[0,\infty)$.

An obvious state space constraint for these models is that the number of cells remains positive. A simple sufficient condition for this to hold is that (*M*) all the matrices $A + \sum_{i=1}^{m} u_i B_i,\ u \in U$, have negative diagonal entries, but non-negative off-diagonal entries (i.e are so-called M-matrices.) In cell-cycle specific compartmental models for cancer chemotherapy which do not consider drug resistance this condition is always satisfied since there are only outflows from the i^{th} compartment, but no direct return flows into the i^{th} compartment. The importance of condition (*M*), however, is more related to the fact that it also implies *negative invariance* of the positive octant under the adjoint flow which describes the evolution of the multipliers in the Maximum Principle. For the models described above, the system matrices no longer are M-matrices. However, it is not difficult to see that states remain positive for all the models introduced above. On the other hand, in the analysis of optimal controls it would be of importance to also have a good *invariance properties of the adjoint flow* and these need to be investigated.

In [24] we already have analyzed necessary conditions for optimality for a general dynamics which satisfies condition (*M*). Since the dynamics and objective are linear in the control variables, the prime candidates for optimality are concatenations of *bang* and *singular controls*. The optimality of possible singular controls needs to be investigated on a case-by-case basis and it is intended to perform such an analysis, possibly investigating whether there exist common features in these models described above which would allow to give a broader criterion. Preliminary computations show that the optimality of singular controls depends on the relative portion of resistant cells, but further analysis needed. Aside from singular controls, bang-bang controls are the natural candidates and typically there will be many trajectories corresponding to bang-bang controls which satisfy the first order necessary conditions for optimality, but are not optimal. In [24] we already developed sharp necessary and sufficient conditions for optimality of bang-bang controls for a general n-compartment model which will be applicable.

3. MATHEMATICAL MODELS FOR CANCER CHEMOTHERAPY WITH MULTIPLE KILLING AGENTS UNDER EVOLVING DRUG RESISTANCE

Over time cancer cells will develop increasing resistance to the killing drug until treatment no longer will be effective. It has been noted in clinical experiments that cancer cells can lose acquired drug resistance through *gene deamplification* in the absence of the drug [1, 8]. However, drug free sessions allow for unrestricted growth of the tumor. Thus an

important therapy strategy is to use *combinations of drugs* in order to prevent that the cancer cells develop too strong a drug resistance to any one of them. Mathematically this leads to a structurally quite different model. Here we introduce such a model for the case of two killing agents. Due to the drugs' interactions the dynamics now will be quadratic in the controls, but with an indefinite structure, and the corresponding Hamiltonian needs to be minimized over a compact control set. These are non-standard, fully nonlinear problems which to the best of our knowledge have not been considered before in this form.

3.1. MODELLING ASPECTS.

We consider two cytostatic killing agents whose dosages are labelled u1 and u2, both with values in the interval [0,1]. (As before, the value 0 represents "no dose" and value 1 corresponds to a "maximum dose"). The state space now is comprised of four compartments, a compartment S of cells sensitive to both drugs, a compartment L_1 sensitive to drug u_1, but resistant to drug u_2, a compartment L_2 sensitive to drug u_2, but resistant to drug u_1, and *a* compartment R of cells resistant to both drugs. We denote the average numbers of cells in these compartments by the corresponding capital Roman letters. As above, it is assumed that the drugs kill a fixed proportion u_1 respectively u_2 of the outflow of the sensitive cells at time t and therefore only the remaining fraction of cells undergoes cell division. If we denote the mean inverse transit times through the compartments by a, b_1, b_2 and c respectively, then, for example, and exactly as above, only a fraction $(1- u_1)(2 - s_1 - r_2)b_1L_1$ of cells from L_1 reenters L_1. Here s_1 is the probability that the second of the two daughter cells becomes resistant also to the second drug u_2, i.e. enters R, and r_2 gives the probability of gene deamplification to go from L_1 into S, i.e. the drug resistance to the second drug u_2 is removed or lost. As above it is assumed that one of the two daughter cells will reenter L_1. However, the terms involving cross-over flows with the sensitive compartment change considerably simply since the two drugs cannot kill the same cell twice. Since the drugs interact with large numbers of cancer cells, it is reasonable to assume that the drugs act independently. Other dependency relations can be postulated, but this will change the return flows to the sensitive compartment. We limit ourselves to making this independence assumption. In this case the return flow is given by $(1- u_1)\ (1- u_2)\ (2 - q_1 - q_2)aS$ and thus becomes quadratic in the controls. In many probabilistic models (e.g. [3]) in order to simplify the analysis similar quadratic terms like $(1- u_1)(1- u_2)$ are linearized with the reasoning that the probabilities involved are small. But for this model such an argument does not apply and is not needed for the tools we intend to use. Overall the dynamics we consider is therefore given as follows:

$$\dot{S} = -aS + (1-u_1)(1-u_2)(2-q_1-q_2)aS + (1-u_1)r_2b_1L_1 + (1-u_2)r_1b_2L_2, \qquad (9)$$

$$\dot{L}_1 = -b_1L_1 + (1-u_1)(2-s_1-r_2)b_1L_1 + (1-u_1)(1-u_2)q_1aS + r_1cR, \qquad (10)$$

$$\overset{*}{L}_2 = -b_2 L_2 + (1-u_2)(2-s_2-r_1)b_2 L_2 + (1-u_1)(1-u_2)q_2 aS + r_2 cR, \tag{11}$$

$$\overset{*}{R} = -cR + (2-r_1-r_2)cR + (1-u_1)s_1 b_1 L_1 + (1-u_2)s_2 b_2 L_2. \tag{12}$$

3.2. THE MODEL AS AN OPTIMAL CONTROL PROBLEM.

In an optimal control formulation of this problem, we again consider the dynamics with an L1-type objective of the form (8). It follows from the necessary conditions of the Maximum Principle [20] that amongst other conditions an optimal control (u_1^*, u_2^*) at every time t minimizes the corresponding Hamiltonian function H over the control set U= [0,1] × [0,1]. While the precise form of H is messy due to the large number of parameters and variables, considered as a function of u_1 and u_2, qualitatively it has the following structure

$$H = \phi(t)u_1 u_2 + \psi_1(t)u_1 + \psi_2(t)u_2 + \chi(t) \tag{13}$$

where φ, ψ_1, ψ_2 and χ all are time-varying functions depending on the states of the system and the costates (or multipliers) arising in the formulation of the necessary conditions for optimality. For sake of argument, for the moment assume φ(t) is positive. Then we need to minimize a function of the form

$$u_1 u_2 - \alpha(t)u_1 - \beta(t)u_2 = (u1-\beta(t))(u2-\alpha(t)) + \alpha(t)\beta(t) \tag{14}$$

over U=[0,1] × [0,1]. Different from any kind of standard formulation in optimal control problems, this quadratic form is indefinite with a saddle point at (α(t), β(t)) and, as can easily be seen, the minimum over the compact and convex set U will always be attained in one of the extreme points of U. Furthermore, except for degenerate situations, the point where the minimum is attained is unique and in these cases the solution is given by

$$(u_1^*(t), u_2^*(t)) = \begin{cases} (0,0) \ if \alpha(t) < 0, \beta(t) < 0 \\ (0,1) \ if \alpha(t) < \beta(t), \beta(t) > 0, \alpha(t) < 1 \\ (1,0) \ if \alpha(t) > \beta(t), \alpha(t) > 0, \beta(t) < 1 \\ (1,1) \ if \alpha(t) > 1, \beta(t) > 1 \end{cases}$$

Possible degeneracies arise in any of the five cases when one of these inequalities is satisfied with equality. Then the minimum value is taken on along a full face of the control set, for example, if α(t) = 0 and β(t) < 0, then the minimum value is 0 and is realized if $u_2 = 0$ regardless of the value of u_1. This is analogous to the case of singular controls for a control linear system and in principle allows the control u_1 to become singular (in the sense that it takes on values in the interior of the interval) while α vanishes identically on some

subinterval. Thus, very much like for the problems described earlier, prime candidates for optimality become bang-bang controls which switch between the vertices of U while singular controls need to be analyzed. There is an interesting switching behaviour as (α, β) crosses the line $\alpha = \beta$ in the first quadrant while α and β both take values between 0 and 1. In such a case the optimal control switches between (0,1) and (1, 0), i.e. both controls switch simultaneously. Medically this corresponds to switching treatment from one drug to the other without having a rest period in between [2].

4. CONCLUSION

This paper presents the formulation and some preliminary analysis of finite-dimensional models describing both phase specificity and drug resistance in cancer chemotherapy. These models provide for an important application of modern control theoretic tools by contributing both to applied aspects of optimal control theory and to giving qualitative insights into designing optimal protocols under drug resistance. Although a restriction to one drug may be oversimplified for practitioners, these studies will form a basis for considering more realistic (but also more complex) models which consider the interactions of several drugs. A main challenge in the mathematical analysis of the model which describes multi-drug chemotherapy will be to establish the range of values for the actual functions $\varphi(t)$, $\psi 1(t)$ and $\psi 2(t)$ in (13). This ultimately defines the controls. Here again it is expected that invariance properties of the adjoint flow will matter and therefore it seems an important issue to develop these properties in greater generality.

The emergence of resistant clones is a universal problem of chemotherapy. However, it seems that its most acute manifestation is the failure to treat metastasis. A part of this problem is the imperfect effectiveness of adjuvant chemotherapy as the tool to eradicate undetectable micrometastases. In view of toxicity of anticancer drugs, optimal scheduling is potentially useful in improving these treatments.

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